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Original Research Article

Comparison of safety and efficacy of tranexamic acid, tranexamic acid with adrenaline, and adrenaline alone in wound infiltration locally for postoperative bleeding in total knee arthroplasty

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ABSTRACT

To compare the efficacies of intra-articular applications of tranexamic acid and adrenaline on postoperative bleeding after total knee arthroplasty. Introduction: Currently, total knee arthroplasty (TKA) is considered the treatment of choice in advanced stages of knee osteoarthritis. Despite advances in surgical and anaesthetic techniques, TKA is still associated with a considerable amount of perioperative blood loss. Tranexamic acid (TXA) is an antifibrinolytic drug whose administration during the perioperative period either by intravenous route or topically applied to the surgical field has been shown to reliably reduce blood loss and need for transfusion in patients undergoing total knee arthroplasty. Material and Method: The single-center, double-blind, controlled study was undertaken after approval from the institutional ethical committee. we included 60 pts in three groups of 20 pts each, Group A pts received 1000mg of tranexamic acid intra-articular and peri-articular, diluted with 10 ml Ns to make it 20 ml, Group B pts received 1000mg tranexamic acid +1 ml of 1:1000 Adrenalin + 9 ml of Ns and Group C pts received1 ml of 1:1000 Adrenalin diluted to 19 ml with Ns at the time of wound closure. We compared blood loss in all the three groups in first 24 hrs, and fall in Hb level from the preoperative level at 4hrs and 24 hrs. post-operatively. Also observed the no of blood transfusions required in all three groups in 48 hrs. Also noted any untoward effects like infection, deep vein thrombosis, etc. Results: Fall in Hb level was also less in Grp B (1.22±0.45), as compared to Grp A (1.56±0.3,) and Grp C (1.65±0.68) at 4 hrs. post-operative and it was statistically significant (P-value 0.0219). Total 24 hrs. fall in Hb was 2.14±0.31 in Grp A, 1.18±1.14 in Grp B, and 2.52±0.19in Grp C which was also statistically significant (P-value 0.005) The total blood loss in 24 hrs. is 324+-81.93ml in Grp B, 370±72.±72.6 ml in Grp A and410.30 ml in Grp C which was statistically significant (P value 0.005). The no of blood transfusion required in 48 hrs. is 5 Units in Grp C as compared to 3 units in Grp A and 2 units in Grp B. Conclusion We came to the conclusion that TXA given as local infiltration is an effective and safe method of preventing postoperative blood loss and the addition of Adrenaline as an adjuvant further adds to its effect without much untoward effect.

1. Introduction

Total knee arthroplasty (TKA) is among the most commonly performed orthopedic procedures. With the aging of the population, increase in life expectancy, and our ability to more effectively manage comorbidities in the perioperative period, the number of people undergoing joint replacement surgery has been steadily increasing over the last decades and that trend is going to continue into the foreseeable future. Only in the US, it is estimated that by the year 2030 almost 3.5 million total knee arthroplasties will be performed annually.[1]

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Orthopedic surgery accounts for a significant proportion of all perioperative packed red-blood-cell transfusions, with arthroplasty accounting for nearly 40% of transfusions in orthopedic patients.[2] It is known that perioperative anemia and RBC transfusions are associated with increased healthcare resource utilization, hospital length of stay, delayed recovery, and higher rates of postoperative morbidity and mortality.[3,4] and its associated complications like transfusion-related haemolytic and non haemolytic reactions, the transmission of diseases, increased risk of infection.

Tranexamic acid intravenously has been extensively studied for reducing post-operative bleeding but its safety regarding venous thromboembolism is a matter of concern[5] Direct local application may reduce systemic toxicity, topical application via haemovac drain has been reported with good results.[5,6] However there is not much data on peri-articular injection of tranexamic acid.[6] The role of EPINEPHRINE in reducing post-operative bleeding has been reviewed lately.[5–8] In this double-blind study, we compared the effect of Trenexa, Adrenaline, and their combined effect on post-operative blood loss.

Since the pioneering work of Hiippala and Benoni and colleagues[9,10] many prospective randomized studies and meta-analyses have confirmed the effectiveness of TXA to reduce perioperative blood loss and the need for allogenic and autologous blood transfusion in patients undergoing TKA.[11]

To address this issue, studies to establish the safety and effectiveness of topical TXA administration have been conducted. The idea is to maximize drug concentration at the site of surgery by intraoperative local infiltration resulting in negligent systemic absorption[12] and by doing so reducing or avoiding completely a generalized antifibrinolytic effect while retaining the beneficial effects of reducing blood loss.[13] In a recently published meta-analysis of 14 randomized controlled trials (11 in knee replacement, two in hip replacement, and one in both) which investigated the effect of topical TXA on blood loss and rates of transfusion Alshryda and colleagues found that indirect comparison of placebo-controlled trials of topical and intravenous TXA indicates that topical administration is even superior to the intravenous route without any significant difference in complication rates.[14]

Tranexamic acid is an antifibrinolytic agent that inhibits the conversion of plasminogen to plasmin and also acts as a plasmin inhibitor thus result in the inhibition of breaking down of fibrin clots and stabilization of clot.[13] Release of tourniquet results in tissue trauma which increases fibrinolysis and plasmin activation The Fibrinolysis peaks at six hours after surgery and maintains at a high rate for up to 18 hours after surgery. Thus, tranexamic acid used in this period can significantly reduce blood loss. TXA reduces blood loss approx. from 10% to 70%.[13,15–20]

Adrenaline exerts its pro-coagulant effect mainly by two aspects 1) it reduces platelet transport time in the spleen and increases platelet aggregation by alpha-adrenergic activity thus resulting in an instant increase in platelet concentration by 20 to 30%.[15,16] epinephrine can promote the release of multiple coagulation factors through beta-adrenergic activation such as fibrinogen.

Intra-articular injection during surgical closure has been recommended for decreasing blood loss following total knee arthroplasty. Adrenaline is associated with some complications like delayed wound healing, skin necrosis, haematoma, and deep vein thrombosis[18,19] and combined effects of TXA and ADRE reduces these effects.

2. Material and Methods

The study was conducted after obtaining institutional ethical committee approval as a randomized double-blind controlled study. Informed written consent was obtained from all patients after thorough explanation.60 patients of ASA gr 1,2, and 3 are included in the study (as elderly pts generally have high B. P and diabetes). Pts with uncontrolled HT, DM, anemia (Hb <9 gm%), cardiac pts (M.I, Arrhythmias), Asthma pts, Pts with h/o thrombo-embolism, or on anticoagulant therapy, and also pts of chronic renal failure are excluded from the study.

Pts are randomized into three Grps. of 20 pts each according to computer-generated random no, kept in separate sealed envelopes. Grp A: pts received TXA 1000 mg (10-15 mg /kg iv 10 ml) +NS10.0 ml to make it 20ml to be given intraarticular and periarticular by surgeons at the time of wound closure before deflation of tourniquet. Grp B: pts received TXA 1000 mg (10 ml) +Adre 1 ml (1:10,000) + NS 9 ml to make it 20 ml. Grp C pts received Adre 1 ml (1:10,000) +NS 19 ml to make it 20 ml.

An Anaesthetist not involved in the conduct of anaesthesia and post-operative management prepared the drugs and gave them to the surgeon to be given intraarticular and periarticular at the time of wound closure before deflation of tourniquet. A blind observer assessed the pts for postoperative bleeding in romovac drain in the first 24 hrs., fall in Hb levels, no. of blood transfusion required in 24 to 48 hrs. and any untoward effects like haemarthrosis, skin redness, necrosis, etc.

All pts were undergone PAC before surgery which included thorough history, GPE, systemic examination, routine investigation including complete hemogram, platelet count, coagulation profile, E.C.G, X-ray chest, S Urea, Cr, and any specific investigation required before surgery. Pts with Hb < 9gm % raised urea- Cr were excluded from the study. All pts were given Spinal Anaesthesia for surgery.

Pts were given 1lit of RL/Ns before the conduct of anaesthesia. Monitoring of Pts started after shifting to O.T., which included B.P. ECG, oxygen saturation (Sp02). After proper painting and draping spinal anaesthesia was given

at L2-L3 or L3-L4 space with all aseptic precautions in sitting position. Inj. Bupivacaine with or without Tramadol was given by Intrathecal route to provide anaesthesia for 3 to 4 hrs. All pts after turning supine were given Inj. Mephentermine 6 mg as prophylactic and further 6 mg were given if there is a fall in B. P< below 90 mm of Hg or a fall of > 30mm of Hg. Pts were given either RL or NS usually 1000 to 1500 ml (10-15 ml /kg/hr.)

2.1. Sample size calculation

We followed the pilot study[13] in which they calculated a sample size based on the measured postoperative blood loss. They assumed an alpha error of 0.05 and applied an allocation ratio of 1. A sample size of 30 participants, which allowed a dropout rate of 10% (3 participants) was calculated to provide an 80% power in detecting a difference of 100-150 ml or reducing postoperative blood loss by 30%in favor of the peri-articular TXA injection. We divided pts into three groups of 20 pts each as we were comparing two drugs individually and their combined effect. All statistical analyses were performed using SPSS software version 17.0 (SPSS Inc, Chicago, IL, USA). Differences in categorical variables were analyzed by chi-square or Fisher's exact test, as necessary, and the unpaired 't' test was used for normally distributed continuous variables.

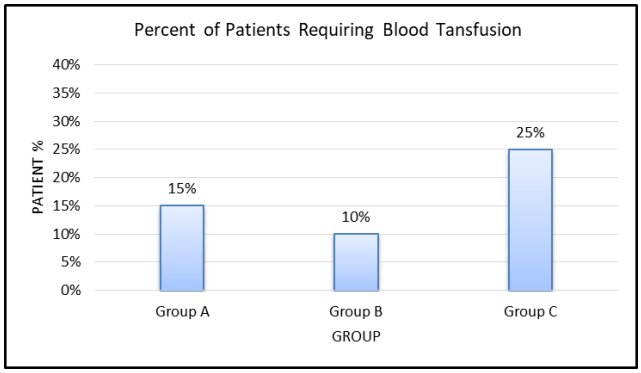

Fig. 1: Percent of patients requiring blood transfusion

3. Observations

There was not much difference in demographic data as observed pre-operatively and is not significant statistically. (P value>0.05) Duration of surgery was also within 90 to 120 min, well done under required tourniquet time, only in 2 pts Surgery was prolonged hence we have to remove the tourniquet and reapply it but still, blood loss was not much and no pt. was given an intraoperative blood transfusion. Post-operatively HR and B.P were comparable in all the three Grps. in 0-4 hrs. but in 4 -8 hrs. HR and B.P was more stable in Grp B (96.66, 108/76;96.56,110/72 ;97.19, 112/76) as compared to Grp A (106.21, 100/72; 104.52, 102/68; 110,100/68) and Grp C(98.56 90.5/74,92.26 96/70,98.52 96/70 which was statistically significant. (P-Value 0 0.054, 0.011; 0.025, 0.010;) After that it was not comparable and non-significant statistically (P-value > 0.05,0.596,0.185;0.835,0.305) Fall in Hb level was also less in Grp B (1.22+-0.45), as compared to Grp A (1.56±0.3) and Grp C(1.65±0.68) at 4 hrs. post-operative and it was statistically significant (P-value 0.0219). Total 24 hrs. fall in Hb was 2.14±0.31 in Grp A, 1.18±1.14 in Grp B, and 2.52+-0.19in Grp C which was also statistically significant (P-value 0.005). as shown in Table 5 The total loss of blood in 0-2 hrs. was 90.76ml in Grp A, 96.6 ml in Grp B and110.6 ml in Grp C. In 2-4 hrs. it is 100ml in Grp A, 84.56 ML IN Grp B, and 130.59 ml in Grp C which was statistically significant. (P value0.0018) The total blood loss in 24 hrs. is 324±81.93ml in Grp B, 370±72. ±72.6 ml in Grp A and 410.30 ml in Grp C which was statistically significant (P value0.005). The no of blood transfusions required in 48 hrs. is 5 Units in Grp C as compared to 3 units in Grp A and 2 units in Grp B. This shows that local infiltration of TXA is effective in reducing postoperative blood loss and the addition of Adrenaline to TXA further helps in reducing the blood loss we didn't observe any untoward effects like pulmonary embolism, DVT, but we didn't perform any radiological or haematological interventions as no pts showed any clinical sign and symptoms. Adrenaline infiltration caused mild tachycardia and rise in B.P but that was transient and lasted only for 5-10 min

4. Discussions

Total knee arthroplasty is an effective treatment for osteoarthritis of the knee. We have seen that pts requiring TKA are elderly (average age ranges from 60-65yrs) and it's a major surgery associated with substantial blood loss, which delays wound healing and may require post-operative allogenic blood transfusion which has complications like allergic reactions, haemolytic or non haemolytic febrile reactions, transfusion-related ALI, Graft Vs host disease, immune-related transfusion reaction, etc. Also, there is an impact on the liver, and chances of transmission of diseases are also there. This blood loss in the post-operative period is there even after improvement in surgical techniques and a decrease in operative time. This necessitates the proper effective and safe measures to reduce post-operative bleeding which helps in early ambulation of these pts and thus reduces morbidity & mortality and decreases the hospital stay time. Many methods have been proposed to reduce perioperative blood loss and preserve haemodynamic stability in these pts. There are various methods of blood loss reduction Antifibrinolytics, Fibrin Glue, Thrombin –Gelatin Mixture, Factor 8 Concentrate[21,22] but none is very established and they are expensive also. Local infiltration of TXA is a safe and inexpensive one and require not much

Table 1: Demographic data

Particulars	Group A		Group B		Group C		P-value
	Mean	Std	Mean	Std	Mean	Std	
Weight	55.18	14.57	60.5	12.9	58.3	12.4	0.6418
Age	60.15	7.6	58.46	9.3	59.25	10.2	0.8417
M/Fm Ratio	19:01		17:03		18:02		
Heart Rate	90.36	5.35	91.46	4.38	90.59	4.35	0.7395
B.P(Sys)	96.56	25.55	98.23	24.9	99.45	12.3	0.9148
B.P(Dias)	80.35	13.56	78.45	12.6	81.59	14.9	0.7355
Hb Level	11.59	2.52	10.72	3.57	11.02	2.95	0.533

Table 2: Comparison of heart rate in the post-operative period

Hr.	Group A		Group B		Group C		P value
0	Mean	Std	Mean	Std	Mean	Std	
0	92.16	3.61	90.05	2.56	91.59	3.5	0.1153
2	96.16	5.15	92.26	4.59	93.39	5.8	0.059
4	94.21	6.59	96.56	3.3	98.56	6.19	0.0541
6	104.52	13.37	96.66	14.06	92.26	14.56	0.0251
8	96.59	12.98	94.19	13.13	98.52	14.13	0.596
12	93.46	13.52	90.32	14.13	91.21	13.14	0.7545
16	91.59	14.16	93.39	13.45	94.21	14.67	0.8353
20	88.92	15.78	90.24	14.67	91.59	13.78	0.8496
24	90.45	13.86	91.56	13.12	92.22	14.11	0.9186

Table 3: Comparison of blood pressure in the post-operative period (systolic)

	Group A		Group B		Group C		P-value
Hr.	Mean	std	Mean	Std	Mean	Std	
0	102.59	5.591	110.59	13.12	96.55	10.95	0.0062
2	110.56	12.19	110.23	14.59	98.76	14.17	0.0117
4	94.56	5.16	93.16	3.13	90.65	3.36	0.0105
6	100.37	7.56	98.22	6.67	96.59	4.56	0.181
8	93.59	5.98	94.46	6.16	96.36	5.12	0.3075
12	1O9.21	14.56	110.42	12.56	112.56	13.24	0.7297
16	116.59	13.59	112.56	14.92	108.67	13.56	0.219
20	111.56	15.17	108.44	19.05	105.67	16.14	0.5466
24	116.34	15.67	110.56	13.75	112.46	17.56	0.5004

Table 4: Comparison of blood pressure in the post-operative period (diastolic)

	Group A		Group B		Group C		P-value
Hr.	Mean	Std	Mean	Std	Mean	Std	
0	80.15	12.19	76.95	13.57	82.19	13.33	0.4454
2	80.2	8.53	76.53	9.56	80.46	10.15	0.345
4	76.25	7.15	74.58	5.76	72.36	8.12	0.2274
6	74.55	13.56	74.36	14.24	70.56	14.34	0.6013
8	76.21	14.63	78.15	14.78	70.48	14.78	0.2394
12	84.32	14.59	80.36	13.96	74.44	14.12	0.0959
16	88.1	13.62	82.15	14.05	76.12	13.78	0.0293
20	88.45	15.73	84.36	15.5	78.2	14.16	0.1074
24	90.15	14.12	88.42	14.19	78.76	13.78	0.0276

Table 5: Hb levels and fall in Hb levels

	Group A		Group B		Group C		P-value
	Mean	Std	Mean	Std	Mean	Std	
Hb (Pre-operative)	11.59	2.52	10.72	3.56	11.02	2.95	0.7143
Hb (Post-Operative)							
4hr	11.01	2.46	10.76	3.05	10.15	2.56	0..5400
24hrs	9.45	2.22	9.54	2.45	8.5	1.97	0.2687
Fall from post-operative Levels							
	1.56	0.3	1.22	0.45	1.65	0.68	0.0219
Fall from pre-operative Levels							
	2.14	0.3	1.18	1.11	2.52	0.19	0.005

Table 6: Blood loss in 24 hrs.

	Group A		Group B		Group C		P-value
Hr.	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**	
0-2	90.76	10.8	88.4	11.21	94.56	10.77	0.2076
.2-4	100.6	13.6	90.56	14.3	106.46	12.56	0.0018
.4-6	70.56	13.56	64.54	11.67	80.56	14.54	0.0014
.6-8	52.5	15.23	50.12	15.14	64.36	16.36	0.0119
.8-12	30.76	28.59	30	27.23	44.18	30.21	0.2247
.12-24	30.54	10.56	30.12	8.93	34.12	11.23	0.4069
Total Blood Loss in 24 hrs.							
24	370.76	72.6	324.54	81.93	.410.35	88.23	0.0005

expertise.

Lin et al.[23] recently published an interesting study introducing the concept of combining two modes of TXA administration. They randomized 120 patients undergoing primary TKA into three groups. One group received a single 1.0 g dose of TXA in 20 mL saline intra-articularly after joint capsule closure (topical group); the second group received a combination of intravenous injection of 1.0g TXA 15 minutes before skin incision followed by local intra-articular application of 1.0 g after joint capsule closure, and the third group received only 20 mL normal saline by local intraoperative infiltration (control group). Outcome parameters were postoperative hemoglobin levels, Hb drop calculated as the difference between preoperative and Hb values at postoperative days 1 and 3, total drain amount at24 h after surgery, calculated total blood loss and transfusion rate. As expected, the mean total blood loss was significantly lower in both the topical and combined groups compared to placebo (705.1±213.9 vs. 578.7±246.9 vs. 948.8±278.5 ml, respectively; P<0.001) as was total drain amount (110.9±61.3vs. 56.8±34.6 vs. 211.9±121.9 mL; P<0.001). There was also a significant difference in transfusion rates when comparing the two TXA groups to controls (3 vs. 0 vs. (12.5±79.1 vs. 0 vs. 62.3±167.4 mL; P=0.008). There was no significant difference when comparing mean total blood loss among the two TXA groups although there is a trending favor of the combined regimen (P=0.063). The same holds when comparing transfusion rates.

Tranexamic Acid is a synthetic analogue of amino acid Lysine that inhibits fibrinolysis thus decreasing blood loss. It is a competitive inhibitor of plasminogen activation and at much higher conc. is a noncompetitive inhibitor of plasmin. Thus, it inhibits fibrinolysis and prevents the breakdown of clots, and reduces blood loss. Intravenous TXA has a proven track record in various surgeries like TKA, THA, Spine surgery[12,13,16–18,24]

There are various studies conducted on local infiltration of TXA in TKA, Comparison of local Vs intravenous TXA.[13] A comparison of TXA and ADRE for local infiltration was done in a study recently and they found encouraging results. They used TXA 3 gm locally for intraarticular and periarticular inj. and compared it with local ADRENALINE inj. 1:2,00,000(1 ml adre 1:1000 dissolved in 200 ml of NS) and found a significant reduction in postoperative blood loss and transfusion requirements.[1–6] In another study, local infiltration was found better than intravenous and is associated with increased efficiency and fewer side effects.[20,25] Drakos et al. in 2016 gave 3 gm. of TXA in intertrochanteric fractures treated with intramedullary nailing. They found a 43% reduction in transfusion requirements.[26]

In the present study, we compared the haemostatic effects of TXA and Adrenaline alone and in combination. We found there is a significant reduction in postoperative bleeding in Grp A (TXA alone) and also effect was better when

we combined the TXA and ADRE (Grp B) as compared to Grp C (ADRE alone). Total blood loss in 24 hrs. was 370.76 ml in Grp A, 324.54 ml in Grp B, and 410.30 ml in Grp C, which was statistically significant (P-value 0.005). Also, pre-operative Hb levels were 11.59±2.52,10.72±3.56 and 11.02±2.95, in the three groups and were statistically insignificant. (P-value 0.5333). post-operative fall in Hb level was 2.14±0.3gm% in Grp A, 1.18±1.1 gm % in Grp B, and 2.52±0.19gm% in Grp C, which was also statistically significant. (P-value 0.005). In our study pts were haemodynamically stable except 4 pts. in Grp C who had significant blood loss and had tachycardia, this indicates that infiltration of Adrenaline alone is not very effective but when given with TXA as adjuvant it increases its clot stabilizing effect.[5] Adrenaline is associated with some untoward effects like haemarthrosis, redness, and skin necrosis at the site of injection[15,19] but we didn't notice any untoward incidence and there was no sign of any DVT in any pts as we gave low molecular weight heparin subcutaneous to all pts 6hrs after surgery and continued 12hrly for 5days and lower limb muscle contraction exercises were initiated as soon as possible after the surgery. Blood transfusion was made only when Hb levels were below 8 or 8.5 gm/dl and pts within Hb levels of 8-10 gm/dl were observed for other signs like tachycardia, palpitation dizziness, etc. If these signs are present and blood loss was significant or the age of the pt. is above 65 pts were given transfusion even at a higher Hb level.

5. Conclusions

By studying the work done by other authors and analyzing our data we came to the conclusion that TXA given as local infiltration is an effective and safe method of preventing postoperative blood loss and the addition of Adrenaline as an adjuvant further adds to its effect without much untoward effect.

6. Drawbacks

In our study, the sample size selected is small hence not able to establish the effects. Therefore we suggest further studies on a large sample size. Also, we followed pts. for 48hrs. Only hence not able to detect untoward effect after 48hrs.

7. Financial Support and Sponsorship

Nil.

8. Conflicts of Interest

Nil.

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